PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
119649.2 LK		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL99/00485	08/09/1999	11/09/1998
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant GARDINO INVESTMENT N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/04/2000	19.12.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Kalsner, I Telephone No. +49 89 2399 8708

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL99/00485

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-45 as originally filed

Claims, No.:

1-28 with telefax of 05/12/2000

Drawings, sheets:

1/15-15/15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☒ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-7, 12, 16, 21, 26, 28 completely; 8, 9, 17, 18, 27, partially.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8, 9, 12, 17, 18, 21, 25-28
	No:	Claims	1-7, 16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	8, 9, 12, 17, 18, 25-28

Industrial applicability (IA) Yes: Claims 1-28
No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Ad Section IV: Lack of unity of invention

An international application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same special technical features, special technical features being such features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

For references to the documents referred to, please see Section V.

The following five inventions have been identified:

Invention I: **Claims 1-7, 16, 28** relating to a DNA sequence coding for oncofetal ferritin 1 (OFF1), a DNA sequence complementary to said sequence, expression vectors comprising said sequences, a method for isolating said sequence and primers derived from said sequence.

Invention II: **Claims 10, 11, 19, 20, 22, 23, and partially, claims 8, 9, 17, 18 and 27**, relating to pharmaceutical compositions for immunisation against and treatment of cancer as well as a method for the diagnosis of cancer.

Invention III: **Claims 12, 21, 25, 26, and partially, claims 8, 9, 17, 18 and 27**, relating to pharmaceutical compositions for the treatment of transplant rejections, autoimmune diseases, pathological pregnancies, for enhancing fertilisation rates during IVF treatment, for induction of abortion and a method for the detection of pathological pregnancies.

Invention IV: **Claims 13-15 and partially 8 and 9**, relating to oncofetal ferritin as a growth factor for bone marrow progenitor cells.

Invention V: **Claims 24 and partially claim 27** relating to a method for the detection of Downs' Syndrome.

The technical relationship between the subject-matter of these groups of claims appears to be the DNA sequence coding for oncofetal ferritin 1 as defined in claim 1.

This DNA sequence, however, is not considered novel over the prior art (D1 discloses cDNA clones for human ferritin H and L chains isolated from human liver cDNA library. The DNA sequences are at least partly identical with the sequences disclosed in Fig. 1 and 4 of the present application.)

Moreover, it is well known in the state of the art, that oncofetal ferritin is involved in various diseases and the protein has been used as a marker protein for pathological pregnancy (D3), cancer (D2) or immunosuppression (D5). Hence, the fact that oncofetal ferritin is involved in various diseases and can be use d for treatment or diagnosis of such diseases cannot be accepted either to constitute a special technical feature as defined above as it does not define a contribution which each of the different claimed inventions, considered as a whole, makes over the prior art.

Thus, the presently claimed subject-matter falls apart in the above groups of inventions which are not unitarian.

As the applicant payed one additional fee for invention III examination was restricted to **claims 1-7, 16, 28, 29** (invention I), **claims 8, 9, 12, 17, 18, 21 and 21-26** insofar as they are related to pharmaceutical compositions for the treatment of transplant rejections, autoimmune diseases, pathological pregnancies, for enhancing fertilisation rates during IVF treatment, for induction of abortion and a method for the detection of pathological pregnancies (invention III).

Ad Section V: Reasoned statement with regard to novelty, inventive step or industrial applicability

1) Amendments

The amendments filed with the letter of 5. December 2000 are allowable under Art. 34(2)(b) PCT. Applicant's comments filed with the letter of 30 October 2000 have been taken into account.

2) Documents

D1...Boyd et al. (1985) J. Biol. Chem. 260:11755-11761
D2...US 4 882 270
D3...WO-A-89 09936
D4...Fisch et al. (1996) Placenta 17: 247-251
D5...US 5 571 678

3) Novelty

3.1) **Claims 1-7 and 16** do not meet the requirements of Art. 33(2) PCT in view of D1.

D1 discloses cDNA clones for human ferritin H and L chains isolated from human liver cDNA library. The DNA sequences are at least partly identical with the sequences disclosed in Fig. 1 and 4 of the present application.

Claim 1 refers (among other things) to fragments of the sequences depicted in Fig. 1 and 4 as well as to DNA sequences that hybridise to the sequences of Fig. 1 and 4. The sequences disclosed in D1 can be considered such fragments or hybridising DNA sequences and are thus novelty destroying for **claims 1-7 and 16** as presently worded.

3.2) **Claims 8, 9, 12, 17, 18, 21 and 25-29** are considered to meet the requirements of Art. 33(2) PCT as the subject-matter of these claims is not disclosed as such in the available prior art.

4) Inventive step

Claims 8, 9, 12, 17, 18, 21 and 25-29, however, do not to meet the requirements of Art. 33(3) PCT for the following reasons:

4.1) **Claims 8, 9, 17 and 18** do not meet the requirements of Art. 33(3) PCT as the provision of pharmaceutical compositions comprising known substances is not considered to involve an inventive step.

4.2) **Claim 12** relates to a pharmaceutical composition for the treatment of transplant rejections, autoimmune diseases, pathological pregnancies and for enhancing fertilisation rates during IVF treatment. It is known in from the prior art (e.g. D4, D5), that low levels of oncofetal ferritin are associated with pathological pregnancies or early abortions in pregnancies induced by IVF. Pharmaceutical compositions comprising known vectors or DNA sequences for the treatment of such conditions are thus not considered to involve an inventive step.

4.3) **Claim 21** is not considered to meet the requirements of Art. 33(3) PCT in view of D4. It is reported in D4 that it was found in an animal model that immunisation of mice with human oncofetal ferritin resulted in abortions (p. 250, right col., lines 8-10). Hence, a pharmaceutical composition comprising an expression vector or an anti-sense mRNA derived from the DNA sequence encoding oncofetal ferritin for the induction of abortion is not considered to involve an inventive step.

4.4) **Claims 25-27** relate to a method for the detection of pathological pregnancies. As it is known in the state of the art that low levels of oncofetal ferritin are indicative for pathological pregnancies (D3, p.6, lines 30-32; example 6) methods for the detection of pathological pregnancies comprising detecting decreased levels of mRNA transcribed from DNA sequence encoding oncofetal ferritin cannot be considered to involve an inventive step.

4.5) **Claim 28** is directed to a method of isolating the DNA sequence of Fig. 1 and 4. A method for isolating a DNA (which has been at least partly disclosed in the prior art (D1) and which, in addition, is not further specified, is not considered to involve an inventive step.

Ad Section VIII: Certain observations on the international application

Claim 28 does not meet the requirements of Art.6 PCT. The claim refers to a method for isolating the DNA sequence of Fig. 1 or 4 "as herein described before". It is not clear to which claims claim 28 refers as none of the preceding claims relate to a method for isolating a DNA sequence. It should be noted that claims shall not rely on references to the description (Rule 6.2(a) PCT).